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MAJOR ARTICLE

High Prevalence of Anal and Oral High-Risk Human Papillomavirus in Human Immunodeficiency Virus–Uninfected French Men Who Have Sex With Men and Use Preexposure Prophylaxis

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Background. We assessed the prevalence and risk factors of anal and oral high-risk (HR) human papillomavirus (HPV) infection in human immunodeficiency virus–uninfected men who have sex with men (MSM) and take preexposure prophylaxis (PrEP) in France.

Methods. Anal and oral samples were screened by multiplex real-time polymerase chain reaction (Anyplex II HPV 28; Seegene) for HPV DNA.

Results. A total of 61 unvaccinated MSM (mean age, 36.1 years) were enrolled. Anal HPV and HR-HPV prevalences were 93.4% and 81.9%, respectively, and oral HPV and HR-HPV prevalences, 33.9% and 19.6%, respectively. HR-HPV type 33 was the most detected genotype, in both anal and oral samples. Among MSM, 68.8% carried ≥1 anal HPV type targeted by the 9-valent Gardasil-9 vaccine; all oral HPV-positive samples carried ≥1 strain included in the vaccine. Condomless receptive anal intercourse and history of anal gonorrhea were the main factors associated with increased risk for anal HPV infection (adjusted odds ratio, 10.4) and anal infection with multiple HR-HPV genotypes (5.77), respectively. Conversely, having had <10 partners in the last 12 months was associated with decreased risk for anal carriage of both multiple HPV (adjusted odds ratio, 0.19) and HR-HPV (0.17) types.

Conclusion. French MSM using PrEP are at high risk for both anal and oral carriage of HR-HPV that could lead to HPV-related cancers.

Keywords. Anal and oral HR-HPV; France; HIV preexposure prophylaxis; men who have sex with men; sexual risk behavior; sexually transmitted infections.

Preexposure prophylaxis (PrEP) is a biomedical prevention strategy that aims to prevent human immunodeficiency virus (HIV) acquisition by prescribing a once-daily antiretroviral pill to persons with possible high-risk behaviors, such as condomless sexual intercourse [1, 2], especially in men who have sex with men (MSM) [1–5].

MSM constitute a core group at high risk for several sexually transmitted infections (STIs), including HIV, bacterial STI, and human papillomavirus (HPV) infection [6, 7]. Despite significant enhancement in HIV prevention strategies afforded by PrEP implementation, concerns about increased sexual risk behavior in HIV-uninfected MSM are currently emerging as several reports have shown that anal bacterial STIs such as chlamydiasis, syphilis, and gonorrhea are becoming more prevalent in MSM taking PrEP [1, 2, 4, 8–10]. Indeed, the clinical and epidemiological impact of PrEP on new HIV infections could lead to significant changes in MSM sexual behaviors (eg, an increase in condomless anal intercourse and increased numbers of partners), making MSM taking PrEP at high risk for anal STIs [11, 12].

Another growing health problem that could silently rise in this population group is anal infection with high-risk HPV (HR-HPV) and related anal cancers [7, 13, 14]. Previous studies on anal HR-HPV and related diseases in French MSM concerned HIV-infected individuals [15–19]. Philibert and colleagues [17] reported that prevalences of HR-HPV in the pharynx, rectum, and urine of a limited series of 17 HIV-uninfected French MSM not taking PrEP were 29.4%, 70.6%,

Received 22 March 2019; editorial decision 17 June 2019; accepted 18 June 2019.

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DOI: 10.1093/ofid/ofz291

and 0% respectively. Pursuing sexual risk behaviors in HIV-uninfected MSM taking PrEP, such as condomless receptive anal intercourse and an increased number of sexual partners, enhances sexual behavior strongly associated with a high risk of anal HR-HPV in MSM [7, 13, 14]. Furthermore, oral infection by HR-HPV increases the risk of oropharyngeal cancer, and MSM are at higher risk for oral HR-HPV infection than the general population [20].

Because the burden of anal and oral HR-HPV infection in HIV-uninfected French MSM using PrEP remains unknown, we designed a "real world" cross-sectional survey to assess the prevalence and risk factors of anal and oral HR-HPV infection in HIV-uninfected MSM taking PrEP and followed up in French healthcare facilities.

MATERIAL AND METHODS

Study Design

The study was a descriptive, quantitative, cross-sectional survey, using a face-to-face questionnaire, among MSM consulting for PrEP at healthcare facilities in Orléans, France.

Enrollment and Selection Criteria

HIV-infected MSM seeking PrEP at consultation services of the Centre Hospitalier Régional d'Orléans and the Centre Gratuit d'Information, de Dépistage et de Diagnostic (CEGIDD) of Orléans, France, were prospectively enrolled in the study. The outpatient consultation services of the Centre Hospitalier Régional and the CEGIDD provide diagnosis and care of infectious diseases, including HIV infection and STIs, for general adult populations. Furthermore, MSM regularly attend the STI consultation service and the CEGIDD for HIV and STI screening, counseling, and care. PrEP for HIV prevention is prescribed to HIV-uninfected MSM, according to French national recommendations [21].

Inclusion criteria were age >18 years, self-reported MSM status, taking PrEP for ≥12 months, having a medical report from <3 months with a conclusive HIV-negative result, being HIV negative after a new serological HIV diagnostic at inclusion, and having a complete medical and sociodemographic record. Exclusion criteria were age <18 years, being heterosexual, having abandoned PrEP for a long period or permanently, and unwillingness to participate in the study.

At inclusion in the study, a face-to-face standardized interview was conducted by a clinician to collect patient information, including age, marital status, country of origin, number of sexual partners in the last 12 months, frequency of condom use, sexual practices, and history of anal STIs. After the interview, MSM underwent medical appointments, including clinical examinations and biological investigations for STI diagnosis, including testing HIV (to confirm HIV-negative serostatus), syphilis, chlamydia, and gonorrhea. A medical appointment was repeated 1 month after PrEP initiation and every 3 months, as recommended by French national guidelines [21]. MSM who tested positive for bacterial STIs received adapted antibiotic treatment. Test results for HPV were later communicated, and patients were invited to undergo proctologic examination.

Samples and Processing

For anal sampling, a moistened flocked swab (Copan Diagnostic) was inserted into the anal canal and rotated 5 times at the contact of the anal epithelial margin, and its tip was placed in a 5-mL plastic tube containing Cobas polymerase chain reaction medium (Roche Molecular Systems) and transported to the laboratory within 4 hours to be kept frozen at −80°C until molecular analysis. For oral sampling, MSM were asked to gargle for ≥1 minute before providing a sputum sample in a plastic container, which was then stored at −80°C until processing.

HPV Detection and Genotyping

The anal swab and oral sputum samples from each participant were processed using the DNeasy Blood and Tissue kit, as recommended by the manufacturer (Qiagen) for DNA extraction. HPV DNA detection and genotyping were carried out with 5 µL of extracted DNA, using the real-time polymerase chain reaction assay Anyplex II HPV28 detection test (Seegene), as described elsewhere [7, 22].

Statistical Analyses

The statistical analyses were conducted using IBM SPSS Statistics 20 software (IBM, SPSS). Means with standard deviations were calculated for quantitative variables and proportions for categorical variables, and reported along with their 95% confidence intervals. *P* values were calculated using Pearson's χ^2 or Fisher exact tests for categorical variables and the nonparametric Mann-Whitney *U* test for quantitative variables. The HPV outcomes variables (ie, anal or oral infection with any type of HPV, multiple HPV types , any HR-HPV, and multiple HR-HPV types) were computed in univariate and multivariate logistic regression analyses. Crude odds ratios (cORs) and adjusted odds ratios (aORs) were calculated, as appropriate, along with their 95% confidence intervals. Risk factors and protective factors were deducted from cORs, aORs, and *P* values. as described elsewhere [23].

Ethics Statement

The study was formally approved by the Scientific Research Committee of the Centre Hospitalier Régional d'Orléans. Primary prevention of HPV infection by vaccination with the 9-valent vaccine was proposed for young MSM (up to age 26 years) included in the study, as recommended in France [24]. All the included MSM have signed an informed consent before participating to the study.

RESULTS

Study Population

From June to October 2018, 61 unvaccinated MSM consulting for PrEP were prospectively enrolled (Table 1). MSM were generally young adults (mean age, 36.1 years). They mainly originated from France, except for 2 from sub-Saharan Africa and 1 from South America. They were mostly single (67.2%), and 32.8% were in stable relationships.

At inclusion, the majority of MSM (72.1%) reported having had sexual intercourse with ≥10 partners in the last 12 months; 18 (29.5%) had had ≥50 partners (range, 50–350), and a minority (27.9%) reported having had <10 partners during the last year, including 2 (3.3%) who reported <5 partners. The majority reported both receptive (88.5%) and insertive (73.8%) anal intercourse, and receptive (96.7%) and insertive (86.9%) oral intercourse. Furthermore, the majority (65.6%) reported participating regularly in group-sex parties during, which a minority (16.4%) reported using drugs ("chemical sex") during intercourse.

Only a minority of study participants (21.3%) reported always using condoms during sex; the majority (75.4%) reported inconsistent use of condoms, including 2 participants (3.3%) who reported never using a condom during sex. Finally, most participants reported a history of bacterial anal STIs, with anal gonorrhea most frequently reported (39.3%), followed by anal syphilis (32.8%) and anal chlamydiasis (22.9%). Nearly one-fifth of participants (19.7%) reported having previously contracted ≥2 bacterial STIs.

HPV Prevalence, Genotype Distribution, and Presumed Predictive Efficiency of Prophylactic 9-Valent HPV Vaccine

HPV molecular results in anal swab and oral rinse samples are shown in Table 1. The prevalence of anal HPV in study MSM was 93.4% (57 of 61). Anal carriage of HR-HPV was particularly frequent, with a prevalence of 81.9% (50 of 61). Anal infection with multiple HPV genotypes was also very frequent (73.8%) and nearly half (44.3%) of MSM harbored infection with multiple HR-HPV genotypes, with an average of 3.1 HR-HPV genotypes (range, 2–6) per anal sample.

Figure 1 depicts a high heterogeneity in the distribution of HPV genotypes in anal sample positive for HPV DNA, with HR-HPV type 33 (31.14% [19 of 61]) the predominant genotype. Along with the HPV-33, HPV-42 (27.8%), HPV-53 (24.6%), HPV-51 (19.7%), HPV-6 and HPV-70 (18.1%) were the 6 most detected genotypes in anal samples. HPV-16 and HPV-18 were detected with a prevalence of 16.4% and 9.8%, respectively. The other high-risk types included in the 9-valent vaccine (Gardasil-9; Merck) were detected at the following prevalence rates: HPV-52, 16.4%; HPV-58, 14.8%; HPV-45, 11.5%; and HPV-31, 9.8%. The HR-HPV types 68 (13.1%), 56 (11.5%), 35, 39 (9.8%), and 59 (3.3%) were also detected. Finally, several low-risk-HPV types were also detected.

Table 1. Baseline Characteristics of the 61 Study Men Who have Sex With Men Taking Preexposure Prophylaxis and Living in Orléans, France

Characteristics	MSM, No. (%) [95% CI]
Age, y	
19–29	21 (34.4) [22.5–46.3]
30–39	17 (27.9) [16.6–39.1]
40–49	15 (24.6) [13.8–35.4]
≥50	8 (13.1) [4.6–21.6]
Origin	
Europe (France)	58 (95.1) [89.6–100.0]
Sub-Saharan Africa	2 (3.3) [.0–7.7]
South-America	1 (1.6) [.0–4.8]
History of anal STI	
Syphilis	20 (32.8) [21.1–44.6]
Gonorrhea	24 (39.3) [27.1–51.6]
Chlamydiasis	14 (22.9) [12.4–33.5]
≥2 Anal STIs	12 (19.7) [9.7–29.6]
Marital status	
Single	41 (67.2) [55.4–78.9]
Living in couple	20 (32.8) [21.1–44.6]
No. of male sexual partners in last 12 mo	
<5	2 (3.3) [.0–7.7]
5–10	15 (24.6) [13.8–35.4]
10–49	26 (42.6) [30.2–55.1]
≥50	18 (29.5) [18.1–40.9]
Frequency of condom use during sex	
Always	13 (21.3) [11.1–31.6]
Sometimes	46 (75.4) [64.6–86.2]
Never	2 (3.3) [.0–7.7]
Sexual practices in last 12 mo	
Receptive anal sex	54 (88.5) [80.5–96.5]
Insertive anal sex	45 (73.8) [62.7–84.8]
Receptive oral sex	59 (96.7) [92.2–100.0]
Insertive oral sex	53 (86.9) [78.4–95.4]
Chemical sex[a]	10 (16.4) [7.1–25.7]
Engaged in group sex	40 (65.6) [53.6–77.5]
HPV DNA detection and types in anal canal	
HPV DNA in swab sample	57 (93.4) [87.2–99.6]
Multiple types of any HPV	45 (73.8) [62.7–84.8]
LR-HPV	40 (65.6) [53.6–77.5]
Possibly oncogenic HPV	23 (37.7) [25.5–49.9]
HR-HPV	50 (81.9) [72.3–91.6]
Multiple types of HR-HPV	27 (44.3) [31.8–56.7]
Any 9-valent vaccine types[b]	42 (68.8) [57.2–80.5]
Multiple 9-valent vaccine types	27 (44.3) [31.8–56.7]
Any 9-valent vaccine HR-HPV types	41 (67.2) [55.4–78.9]
Multiple 9-valent vaccine HR-HPV types	22 (36.1) [24.1–48.1]
HPV DNA detection and types in oral secretions[c]	
HPV DNA	19 (33.9) [21.5–46.3]
Multiple types of any HPV	4 (7.1) [.4–13.9]
LR-HPV	5 (8.9) [1.4–16.4]
Possibly oncogenic HPV	8 (14.3) [5.1–23.4]
HR-HPV	11 (19.6) [9.2–30.1]
Multiple types of HR-HPV	3 (5.4) [.0–11.2]
Any 9-valent vaccine types	11 (19.6) [9.2–30.1]
Multiple 9-valent vaccine types	2 (3.6) [.0–8.4]
Any 9-valent vaccine HR-HPV types	10 (17.8) [7.8–27.9]
Multiple 9-valent vaccine HR-HPV types	2 (3.6) [.0–8.4]

Abbreviations: CI, confidence interval; HPV, human papillomavirus; HR-HPV, high-risk-HPV; LR-HPV, low-risk-HPV; MSM, men who have sex with men; STI, sexually transmitted infection.

[a]Chemical sex is defined as sexual intercourse under the influence of a drug.

[b]The 9-valent vaccine (Gardasil-9; Merck) is effective against HPV genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58.

[c]Five MSM were not able to provide convenient oral secretion samples for HPV detection and were excluded from analysis; HPV types were detected in 56 available oral secretion samples.

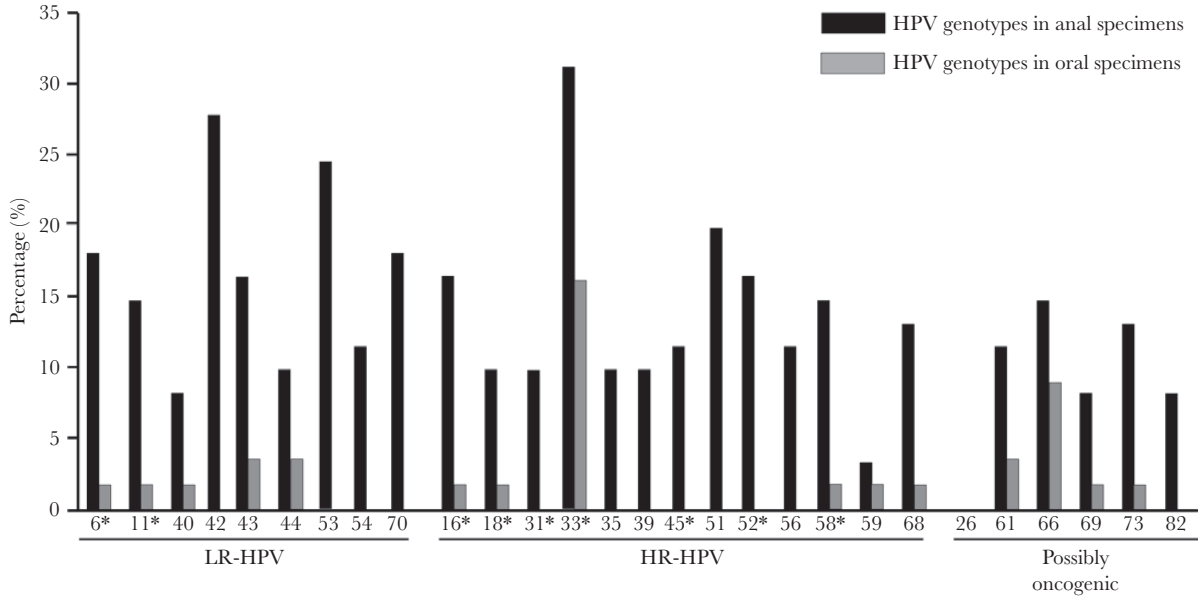

Figure 1. Proportions of human papillomavirus (HPV) genotypes identified by molecular biology in 57 anal and 19 oral samples from young men who have sex with men taking preexposure prophylaxis and living in France. Low-risk (LR), high-risk (HR), and possibly oncogenic HPV genotypes are shown, and genotypes included in the 9-valent (Gardasil-9) vaccine are indicated by asterisks.

The distribution of anal HPV and HR-HPV prevalence according to age is represented in Figure 2. All age groups were highly infected with HPV (95.2% prevalence for ages 19–29 years, 94.1% for 30–39 years, 86.7% for 40–49 years, and 100% for ≥50 years) and HR-HPV (90.5%, 82.3%, 66.7%, and 87.5% for the 4 respective age groups), with no statistically significant difference between groups.

Regarding the oral samples, 5 of the 61 MSM included in the study were not able to provide adequate oral rinse samples and were excluded from HPV analyses. One-third of MSM who provided (33.9% [19 of 56]) were positive for HPV DNA in their oral samples and a minority (7.1% [4 of 56]), had multiple HPV genotypes (Table 1). About one-fifth of MSM (19.6% [11 of 56]) had HR-HPV, and oral HPV infections were caused by multiple HR-HPV genotypes in 3 MSM (27.7%).

As shown in Figure 1, the 9-valent vaccine genotype HPV-33 was the predominant genotype detected in oral samples (in 16.1% [9 of 56]), followed by HPV-66, with a prevalence of 8.9% (5 of 56), HPV-43, HPV-44 and HPV-61 with prevalences of 3.6% (2 of 56) and finally the following genotypes, which were detected only once: HPV-16, HPV-18, HPV-58, HPV-59, HPV-68, HPV-6, HPV-11, HPV-40, HPV-69, and HPV-73.

Figure 2 details the distribution of oral HPV and HR-HPV prevalence according to age. The 4 delimited age groups showed relatively low prevalences of HPV genotypes (47.4% for the age 19–29 years, 23.5% for 30–39 years, 30.7% for 40–49 years, and 28.6% for ≥50 years) and HR-HPV genotypes (26.3%, 17.6%, 23.1%, and 0.0%, respectively). There were no significant differences between age groups.

Among the 19 MSM with oral HPV infection, only 7 harbored similar HPV genotypes in both oral and in anal sites (Table 2), and 1 harbored >2 similar HPV genotypes in both sites. Finally, 17 of the 57 MSM (29.8%) who had anal HPV infections showed oral HPV DNA positivity. More than half of them (52.9% [9 of 17]) had HR-HPV genotypes in both sites.

Risk Factors Associated With Anal and Oral HPV Infection

Associations between anal and oral HPV infection outcomes (ie, infection with any HPV, multiple HPV, any HR-HPV, or multiple HR-HPV genotypes) and their potential risk factors were analyzed by means of logistic regression analysis (Table 3).

For oral HPV outcomes, no association could be found in univariate

analysis. Univariate analyses for anal HPV infection revealed significant association between HPV infection with any genotype and the practice of receptive anal intercourse (cOR, 10.4; $P = .05$), between HPV infection with multiple genotypes and being aged19–29 years (5.1; $P < .05$), and between HPV infection with multiple HR-HPV genotypes and a history of gonorrhea (4.72; $P < .01$). Acquisition of multiple HPV genotypes was less frequent in MSM 40–49 years (cOR, 0.3; $P < .05$). Finally, acquisition of multiple HPV or multiple HR-HPV genotypes was less frequent in MSM aged 40–49 years and in those having had ≤10 different sexual partners in the last 12 months (cOR, 0.3 and 0.23, respectively; $P < .05$).

In multivariate analyses, a reported history of receptive anal intercourse constituted a predictive risk factor significantly associated with anal HPV infection by any genotype (aOR, 10.4; $P < .05$). For anal infection with multiple HPV genotypes, multivariate

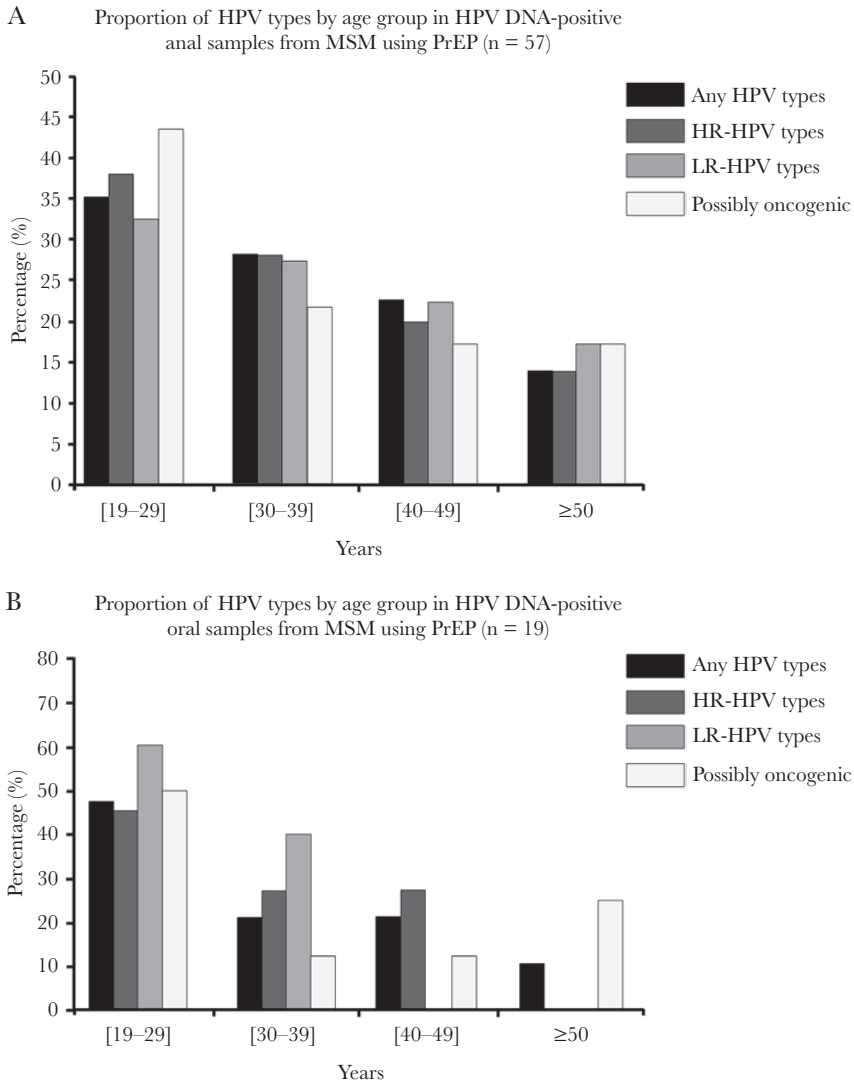

Figure 2. Proportion of human papillomavirus (HPV) genotypes, by patient age, in 57 anal (*A*) and 19 oral (*B*) samples positive for HPV DNA among 61 young men who have sex with men taking preexposure prophylaxis and living in France. Abbreviations: HR, high-risk; LR, low-risk.

analysis revealed that having ≤10 different sexual partners in the last 12 months constituted a protective factor (aOR, 0.19; $P < .05$). However, the effect of age on anal infection with multiple HPV genotypes observed in univariate analyses faded in the multivariate analyses. Multivariate analyses also revealed that a history of anal gonorrhea (aOR, 5.77; $P < .01$) was a predictive factor increasing significantly the carriage of multiple HR-HPV genotypes. Conversely, having had ≤10 different sexual partners in the last 12 months (aOR, 0.17; $P < .05$) was a factor associated with lower anal carriage of multiple HR-HPV genotypes. No other sociodemographic, clinical, and behavioral characteristics of MSM were significantly associated with the 4 anal HPV outcomes.

DISCUSSION

The current cross-sectional study highlights the high burden of anal and oral HR-HPV infections in HIV-uninfected French adult MSM taking PrEP. The prevalences of anal HPV, HR-HPV, and multiple HR-HPV genotypes were remarkably high. Moreover, one-third of study MSM carried oral HPV and one-fifth oral HR-HPV. Finally, more than two-thirds of anal HPV and all oral HPV types detected in this population are included in the 9-valent vaccine, and the oncogenic HR-HPV type 33 was the most frequently detected in both anatomic sites. These findings demonstrate the unsuspected high burden of anal and oral HR-HPV that can be prevented by the 9-valent vaccine, substantiating the national recommendations of HPV prophylactic vaccination in young MSM in France [24]. Finally, anal carriage of HPV and HR-HPV was associated with frequent condomless receptive anal intercourse and a history of anal gonorrhea, indicating possible high-risk sexual behavior. These observations highlight that persistent risky sexual behavior is usual in HIV-uninfected MSM taking PrEP.

Table 2. Distribution of all Human Papillomavirus (HPV) Genotypes and Concordant HPV Genotypes in HPV-Infected Men Who Have Sex With Men According to Anal and Oral Sites

	HPV Genotypes		
Patient No.	Anal Site	Oral Site	Anal/Oral Concordant Genotypes
014	16, 39, 42, 44, 51, 52, 54, 61, 70, 73, 82	33, 44, 66, 68	44
015	11, 31, 33, 39, 42, 45, 68	33,	33
021	53, 56, 66, 70	66	66
022	45, 58	33	None
025	None	16	None
028	6, 33, 35, 42, 43, 44, 58, 66, 68, 69, 70, 73	61, 66	66
030	11, 33, 39, 43, 51, 53, 58, 61, 66, 73	44	None
032	33, 42, 44, 45, 53, 69, 82	66	None
038	6, 33, 54, 56, 82	33	33
045	None	59	None
050	6, 18, 58, 73	33	None
053	11, 16, 33, 42, 43, 44, 53, 59, 61, 66, 68	61	61
055	33, 39, 51, 52, 59	69	None
056	42, 68, 69, 70	11	None
057	56, 61	33	None
059	6, 18, 33, 40, 42, 43, 70, 73	6, 18, 33, 40, 43, 73	6, 18,40, 43, 73
082	51, 52	33, 58, 66	None
105	6, 43, 45, 51, 53	33	None
110	11, 33, 42, 44, 53, 66	43	None

Abbreviation: HPV, human papillomavirus.

A high prevalence of anal HR-HPV (81.9%) was found in the current study. A similar prevalence (70.6%) was previously reported in a short series of 17 HIV-uninfected MSM not taking PrEP and living in Marseille, France [17]. Previous studies assessing the burden of anal HR-HPV in HIV-uninfected MSM worldwide reported prevalence rates ranging from 13.3% to 55.6% [25, 26]. High prevalence of anal HR-HPV detection, similar to those in our study, are mostly reported in HIV-infected MSM [16, 19], who constitute a high-risk population for anal HR-HPV [27, 28].

Increased sexual disinhibition caused by the loss of fear of acquiring HIV could lead to risk taking in HIV-uninfected MSM taking PrEP [29]. Indeed, some authors have reported the possibility of HIV risk compensation in PrEP users leading to increased numbers of sexual partners and condomless anal intercourse [9–11, 29, 30].

In addition, prospective studies assessing the incidence of anal bacterial STIs in MSM taking PrEP have reported similar conclusions, highlighting higher incidence rates of anal bacterial STIs along with increased high-risk sexual behaviors in MSM after PrEP initiation, compared with before PrEP initiation [9, 10, 31]. Similarly, a history of anal bacterial STIs was frequently reported in study participants. Significant changes in sexual behavior in MSM taking PrEP become an important risk factor for acquisition of anal bacterial STIs as well as for anal HR-HPV infection [9, 10]. Finally, HR-HPV–infected MSM using PrEP could be at higher risk of high-grade anal squamous intraepithelial lesions and anal cancer because of the syndemic synergy for epithelial transformation previously demonstrated between anal HR-HPV infection and anal bacterial STIs, including anal gonorrhea [32].

Regarding the oral cavity, one-fifth (19.6%) of study MSM were positive for HR-HPV DNA. The previously reported prevalence of oral HR-HPV infection in HIV-uninfected French MSM not taking PrEP was slightly higher (29.4%) [17]. Most previous studies assessing the burden of oral HR-HPV in HIV-uninfected MSM reported prevalence rates ranging from 3.8% to 13.8% [25, 33]. These observations suggest that HIV-uninfected MSM living in France, and particularly those taking PrEP, could be at higher risk of oral HR-HPV infection and possibly oropharyngeal cancer than such MSM in other countries.

Concerning HPV genotype distribution, almost 70% of anal HPV and 100% of oral HPV genotypes were targeted by the prophylactic 9-valent HPV vaccine, which is the basis of the rationale for introducing primary prevention against anal and oral cancer in young HIV-uninfected MSM taking PrEP, by using prophylactic vaccination. Unexpectedly, HPV-16 and HPV-18 were, respectively, only the third and sixth most represented genotypes in anal HPV infections among study MSM. Previous studies reported quite different distributions, with HPV-16 the predominant genotype detected in anal and oral samples from HIV-uninfected MSM [17, 34]. Furthermore, the predominance of HR-HPV type 33 in both anal and oral sites of asymptomatic HIV-uninfected MSM has not been previously reported, to our knowledge and may indicate possible regional

Table 3. Univariate and Multivariate Logistic Regression Analyses of Predictive Risk Factors for Anal Human Papillomavirus Infection in 61 Men Who have Sex With Men Taking Preexposure Prophylaxis and Living in Orléans, France

	Any HPV Genotype (n = 57)					Multiple HPV Genotypes (n = 45)					Any HR-HPV Genotype (n = 50)					Multiple HR-HPV Genotypes (n = 27)				
Risk Factor	No. (%)	cOR (95%CI)	*P* Value[a]	[a]OR (95%CI)	*P* Value[a]	No. (%)	[c]OR (95%CI)	*P* Value[a]	aOR (95%CI)	*P* Value[a]	No. (%)	cOR (95%CI)	*P* Value[a]	aOR (95%CI)	*P* Value[a]	No. (%)	[c]OR (95%CI)	*P* Value[a]	[a]OR (95%CI)	*P* Value[a]
Age, y																				
19–29	20 (35.1)	1.62 (.2–16.6)	.57	NA [b]	NA	19 (42.2)	5.1 (1.1–25.2)	.03	2.99 (.5–17.6)	.22	19 (38.0)	2.76 (.5–14.1)	.18	NA	NA	10 (37.1)	1.23 (.4–3.5)	.45	NA	NA
30–39	16 (28.1)	1.17 (.1–12.1)	.69	NA	NA	12 (26.7)	0.80 (.2–2.7)	.48	NA	NA	14 (28.0)	1.1 (.2–4.5)	.64	NA	NA	8 (29.6)	1.17 (.4–3.6)	.51	NA	NA
40–49	13 (22.8)	0.29 (.1–2.3)	.25	NA	NA	8 (17.8)	0.3 (.1–.9)	.04	0.26 (.06–1.2)	.08	10 (20.0)	0.30 (.0–1.2)	.08	NA	NA	5 (18.5)	0.54 (.2–1.8)	.25	NA	NA
≥50	8 (14.1)	NA	.56	NA	NA	6 (13.3)	1.07 (.2–5.9)	.65	NA	NA	7 (14.0)	1.63 (.2–14.7)	.55	NA	NA	4 (14.8)	1.31 (.3–5.7)	.51	NA	NA
Marital status																				
Single	38 (66.7)	0.67 (.1–6.8)	.60	NA	NA	31 (68.9)	1.3 (.4–4.4)	.43	NA	NA	35 (70.0)	1.94 (.5–7.3)	.26	NA	NA	20 (74.1)	1.77 (.6–5.3)	.23	NA	NA
In couple	19 (33.3)					14 (31.1)					15 (30.0)					7 (25.9)				
History of anal STIs																				
Syphilis	19 (33.3)	1.5 (.1–15.4)	.61	NA	NA	16 (35.6)	1.65 (.4–5.9)	.33	NA	NA	19 (38.0)	6.12 (.7–51.7)	.06	NA	NA	10 (37.1)	1.41 (.5–4.1)	.36	NA	NA
Gonorrhea	23 (40.3)	2.03 (.2–20.7)	.48	NA	NA	19 (42.2)	1.60 (.5–5.4)	.32	NA	NA	22 (44.0)	3.53 (.7–18.1)	.11	NA	NA	16 (59.2)	4.72 (1.5–14.2)	.005	5.77 (1.7–19.3)	.004
Chlamydiasis	14 (24.5)	NA	.34	NA	NA	11 (24.4)	1.40 (.3–5.8)	.46	NA	NA	14 (28.0)	NA	.19	NA	NA	8 (29.6)	1.96 (.6–6.6)	.21	NA	NA
≥2 Anal STIs	12 (21.1)	NA	.41	NA	NA	9 (20.0)	1.08 (.3–4.6)	.61	NA	NA	12 (24.0)	NA	.11	NA	NA	7 (25.9)	2.03 (.5–7.3)	.22	NA	NA
No. of sexual partners in last 12 mo																				
<5	2 (3.5)	NA	.87	NA	NA	2 (4.4)	NA	54	NA	NA	2 (4.0)	NA	.67	NA	NA	2 (7.4)	NA	.19	NA	NA
5–9	13 (22.8)	0.29 (.1–2.3)	.25	NA	NA	8 (17.8)	0.3 (.08–.8)	.04	0.19 (.05–.83)	.04	11 (22.0)	0.49 (.1–1.9)	.26	NA	NA	3 (11.1)	0.23 (.01–.9)	.028	0.17 (.04–.8)	.025
10–49	26 (45.6)	NA	.10	NA	NA	20 (44.4)	1.33 (.4–4.3)	.42	NA	NA	21 (42.0)	0.87 (.2–3.2)	.54	NA	NA	12 (44.4)	1.14 (.4–3.2)	.50	NA	NA
≥50	16 (28.1)	0.39 (.1–3.1)	.34	NA	NA	15 (33.4)	2.2 (.5–8.7)	.2	NA	NA	16 (32.0)	2.12 (.4–10.9)	.31	NA	NA	10 (37.1)	1.91 (.6–5.8)	.19	NA	NA
Frequency of condom use																				
Always	13 (22.8)	NA	.37	NA	NA	10 (22.2)	1.24 (.3–5.2)	.54	NA	NA	12 (24.0)	3.15 (.4–27.3)	.25	NA	NA	7 (25.9)	1.63 (.4–5.6)	.31	NA	NA
Sometimes	42 (73.7)	NA	.31	NA	NA	33 (73.4)	0.63 (.2–2.6)	.39	NA	NA	36 (72.0)	0.25 (.3–2.2)	.17	NA	NA	18 (66.7)	0.43 (.1–1.4)	.13	NA	NA
Never	2 (3.5)	NA	.87	NA	NA	2 (4.4)	NA	.54	NA	NA	2 (4.0)	NA	.67	NA	NA	2 (7.4)	NA	.19	NA	NA
Sexual behavior																				
Group sex	36 (63.1)	NA	.17	NA	NA	32 (71.1)	2.46 (.7–7.9)	.11	NA	NA	35 (70.0)	2.80 (.7–10.6)	.12	NA	NA	21 (77.8)	2.73 (.8–8.5)	.06	NA	NA
Chemical sex[c]	9 (15.8)	0.56 (.5–6.1)	.52	NA	NA	8 (17.8)	1.51 (.3–8.0)	.48	NA	NA	9 (18.0)	2.19 (.2–19.4)	.42	NA	NA	6 (22.2)	2.14 (.5–8.5)	.23	NA	NA
Receptive anal sex	52 (91.2)	10.4 (1.2–90.5)	.05	10.4 (1.2–90.5)	.034	41 (91.1)	2.36 (.4–11.9)	.26	NA	NA	45 (90.0)	2.00 (.3–11.9)	.37	NA	NA	26 (96.3)	5.57 (.6–49.5)	.09	NA	NA
Insertive anal sex	42 (73.7)	0.93 (.1–9.6)	.72	NA	NA	33 (73.4)	0.91 (.2–3.4)	.58	NA	NA	38 (76.0)	1.81 (.4–7.3)	.31	NA	NA	20 (74.1)	1.03 (.3–3.2)	.59	NA	NA
Receptive oral sex	55 (96.5)	NA	.87	NA	NA	43 (95.6)	NA	.54	NA	NA	48 (96.0)	NA	.67	NA	NA	25 (92.6)	NA	.19	NA	NA
Insertive oral sex	50 (87.7)	2.38 (.2–26.2)	.44	NA	NA	39 (86.7)	0.92 (.2–5.1)	.65	NA	NA	44 (88.0)	1.63 (.3–9.4)	.44	NA	NA	24 (88.9)	1.38 (.3–6.4)	.49	NA	NA

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; HPV, human papillomavirus; HR-HPV, high-risk-HPV; NA, not attributable; STIs, sexually transmitted infections.

[a]*P* values were calculated using Pearson $\chi 2$ or Fisher exact tests.

[b]Not attributable for variables for which the cOR was not significant in univariate and multivariate analyses ($P > .05$).

[c]Chemical sex is defined as sexual intercourse under the influence of a drug.

clusterization in the spreading of particular HR-HPV genotypes within the French MSM community [7].

In the present series, MSM reporting condomless receptive anal intercourse were 10.4-fold more likely to have anal HPV infection than those reporting exclusively insertive anal intercourse. These findings confirm that the risk of anal STI acquisition is strongly associated with the sexual behavior and the number of sexual partners in the MSM population. Indeed, MSM practicing condomless receptive anal intercourse with male partners are more likely to acquire HIV and anal STIs than those who only practice condomless insertive anal intercourse, with exacerbation in direct relationship to the number of sexual partners [7, 32, 35–38].

Our study has some limitations. Because the presence of HPV was assessed using a single anal sample and a single oral sample both taken 12 months after the start of PrEP, HPV carriage in anal or oral samples could reflect transient infections, persistent infections, or even HPV DNA deposition from a recent sexual partner, as previously demonstrated [39]. Therefore, the results of HPV DNA carriage could theoretically correspond to several situations, although the most plausible is probably an effective mucosal infection by HPV. In addition, HPV DNA carriage could reflect either high-risk sexual behavior before the start of PrEP (leading to the request for PrEP) or high-risk sexual behavior beginning with the use of PrEP. These considerations argue for more nuanced interpretation of study results. On the other hand, the lack of baseline data makes it impossible to precisely assess the causality link between anal HPV infection or bacterial STIs, and the possibility of residual confounding in the analyses. Finally, the limited sample size in our study population and the high prevalence of anal HPV DNA detected in these MSM limit the power to detect risk factors.

In conclusion, the French HIV-uninfected MSM taking PrEP constitute a high-risk population for anal and oral HR-HPV infections that could lead to HR-HPV–related cancers. Although PrEP alone constitutes a promising tool for reducing and preventing HIV in MSM, it remains necessary to associate PrEP with sexual behavioral interventions and education programs, and anal bacterial STI treatment when necessary, regular anoscopy, anal and oral HPV DNA screening, and vaccination with the 9-valent vaccine for eligible MSM.

Acknowledgments

R. S. M. B. is a PhD student from the Ecole Doctorale en Infectiologie Tropicale, Franceville, Gabon, benefiting from a scholarship of the Gabonese Government and from the Agence Universitaire de la Francophonie. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions. R. S. M. B., L. B., A. G., L. H., and T. P. conceived and designed the research; A. G. and T. P. attended to the ethical issues; C. G., A. M., A. G., L. H., and T. P. received and included the study participants and carried out the sampling; R. S. M. B., M. M., and J. P. carried out the experiments; R. S. M. B., S. T. W., and D. V. performed statistical analyses; R. S. M. B., H. P., and S. T. W. analyzed the results; R. S. M. B., L. B., and T. P. drafted the manuscript.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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